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(54) Title: USE OF PROANTHOCYANIDINS AS AN ACTIVE INGREDIENT OF A STIMULATOR AND L-ARGININE OR ITS SALTS AS A SOURCE OF NITRIC OXIDE TO RELIEVE SYMPTOMS OF ERECTILE DYSFUNCTION

(57) Abstract: Use of proanthocyanidins as an active ingredient of a stimulator and L-arginine or its salts as a source of nitric oxide in the treatment of erectile dysfunction. The active ingredient stimulates the endothelial NO-synthase enzyme, which acts as a catalyst for the synthesis of nitric oxide from its substrate L-arginine or its salts. The nitric oxide in turn activates the guanylyl cyclase, which leads to an increased development of cyclic guanosine monophosphate, which causes relaxation of smooth muscles. Blood vessel diameter may increase. The stimulator may also have Sildenafil or enzymes that inhibit an enzyme phosphodiesterase type 5 from reducing an amount of the cyclic guanosine monophosphate.

USE OF PROANTHOCYANIDINS AS AN ACTIVE INGREDIENT
OF A STIMULATOR AND L-ARGININE OR ITS SALTS AS A SOURCE
OF NITRIC OXIDE TO RELIEVE SYMPTOMS OF ERECTILE DYSFUNCTION

5 BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to the use of proanthocyanidins to stimulate the enzyme NO-synthase, which acts as a catalyst to release nitric oxide from L-arginine (or its salts). Such is advantageous in relieving symptoms of erectile dysfunction.

10

Discussion of Related Art

The normal penis reaction is based on a series of neurally mediated changes of bloodstream in the erectile tissue. The condition for an increased blood supply is the relaxation of smooth muscles in the erectile tissue. The relaxation takes place as follows:

15

As a result of sexual stimuli, the enzyme NO-synthase (NOS) gets activated in endothelial cells of the erectile tissue. This enzyme acts as a catalyst for the synthesis of nitric oxide (NO) from its substrate, amino acid L-arginine. The NO in turn activates the guanylyl cyclase which leads to an increased development of cyclic guanosine monophosphate (cGMP).

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The cGMP causes relaxation of smooth muscles. Due to the reduction of cGMP by means of further enzymes, of which the phosphodiesterase type 5 (PDE type 5) is the most important one, the vasodilation can be rescinded.

The male impotence or erectile dysfunction is a widespread problem. It is the persistent inability of a man to get an erection and to maintain it long enough for satisfying sexual

intercourse. The erectile dysfunction occurs mainly in older men; approximately 30% of men in their forties and 67% of men in their seventies are affected.

Present treatments comprise vacuum pumps, penis prostheses, vascular surgery and the use of vasodilatory medicaments, such as Alprostadil, which can either be injected into the
5 erectile tissue (Corpus cavernosum) or be brought into the urethra by means of an applicator. In March 1998, the American health authority FDA approved sildenafil (Viagra) as an oral treatment. In addition, there are other substances that are available that have the same, or substantially the same, mechanism of action as sildenafil. These other substances inhibit phosphodiesterase type 5 and/or prevent the decrease of cGMP.

10 Proanthocyanidins are homogeneous or heterogenous polymers consisting of the monomer units catechin or epicatechin, which are connected either by 4-8 or 4-6 linkages, to the effect that a great number of isomer proanthocyanidins exist. Typically, the procyanidin oligomers have a chain length of 2-12 monomer units.

Proanthocyanidins can be found in vegetable extracts, as well as in extracts of the bark
15 of a maritime pine, the cones of cypresses, and the seeds and skin of grapes. A well-known product containing proanthocyanidins, which is available in trade as a preparation of a food supplement under the name Pycnogenol® , is an extract of the maritime pine bark (Pinus pinaster). The Pycnogenol® food supplement contains approximately 70-80% of proanthocyanidins and is a complex mixture of phenolic substances. It possesses a multitude of
20 interesting and useful biochemical and pharmacological qualities. In particular, it is well known for its protecting effect against aging associated chronic diseases, such as atherosclerosis and its cardiovascular events such as stroke or heart infarction. Besides proanthocyanidins and its monomeric unit catechin, Pycnogenol® food supplement contains taxifolin and a wide range of

phenolic acids, e.g. free acids like p-hydroxybenzoic acid, protoacatechic acid, vanillic acid, caffeic acid and ferulic acid as well as its glucosides and glucose esters. Most of the positive effects of Pycnogenol® are attributed to its antioxidant qualities.

Pycnogenol® food supplement deactivates superoxide radicals and hydroxyl radicals and
5 inhibits the development of other oxygen radicals. In vitro, Pycnogenol® food supplement inhibits the peroxidization of LDL, the fat peroxidization in phospholipid liposomes and the fat peroxidization caused by t-butylhydroperoxide as well as the damage to cells induced by UV-B. As Pycnogenol® inhibits, in particular, the fat peroxidization of LDL, the risk of arteriosclerosis decreases. Moreover, Pycnogenol® food supplement contains procyanidins protecting collagen
10 and elastin against enzymatical decomposition, which has a positive influence on the capillary resistance. The oral supply of this preparation to humans decreases the development of leg oedema.

It is known that some vegetable extracts containing proanthocyanidins show an endothelium-dependent relaxing activity (EDR). This has already been proven in red wine, grape
15 juice and extracts of the peel of grapes ex vivo in aorta rings of rats (Fitzpatrick et al, Am., Physiol, 1993, 265 H774-8). Also, as concerns Pycnogenol® food supplement, such has also been found (Fitzpatrick et al: J Cardiovasc, Pharmacol, Volume 32 Nr. 4, 1998) in that the fractions 3 preserved by sephadex LH-20 exclusion chromatography contained proanthocyanidins with a higher molecular weight showed the strongest EDR. Thus, it had been
20 shown that proanthocyanidins increase the activity of the NO-synthase. The inhibition of the NO-synthase by well known inhibitors has been compensated by means of Pycnogenol® food supplement.

Sildenafil inhibits selectively the phosphodiesterase type 5 and thus prevents the decrease of cGMP. However, as Sildenafil does not promote the development of cGMP, but merely inhibits the decrease of existing cGMP, it is only effective, when there is already a quantity of cGMP sufficient enough for an erection, as for example in case of a strong sexual arousal. In case
5 that there is an insufficient production of nitric oxide, which is necessary for stimulation of cGMP synthesis, the possibility exists that the quantity of cGMP is insufficient for an erection.

It is therefore desirable to develop a stimulation technique which does not interfere with the above mentioned chain reaction at the end, i.e., the prevention of the decrease of cGMP, but has a positive influence on the preceding reactions by stimulating NO-synthase and raising NO
10 and cGMP concentrations.

SUMMARY OF THE INVENTION

One aspect of the invention resides in a stimulation technique that uses a combination of a source of nitric oxide, namely, amino acid L-arginine or its salts, and an active ingredient,
15 namely, proanthocyanidins. Both the proanthocyanidins and the L-arginine or its salts are in therapeutically effective amounts to relieve symptoms of erectile dysfunction and increase blood vessel diameter.

The proanthocyanidins are in an amount sufficient to stimulate the endothelial NO-synthase enzyme. Once stimulated, endothelial NO-synthase enzyme acts as a catalyst to
20 synthesize nitric oxide from its substrate amino acid, L-arginine. Such a stimulator is necessary for the production of cGMP in larger amounts so that after neural activation, the development of nitric oxide may increase. The nitric oxide activates guanylyl cyclase, which increases cGMP and results in relaxation of smooth muscles.

The combination may also have sildenafil or an inhibitor that inhibits an enzyme phosphodiesterase type 5 from reducing an amount of the cGMP. In addition, both proanthocyanidins and L-arginine may be taken simultaneously. For instance, if both are in oral dosage form, both would be swallowed and be present within the stomach at the same time.

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DETAILED DESCRIPTION OF THE INVENTION

Due to its content of proanthocyanidins, Pycnogenol® food supplement - and other vegetable extracts containing proanthocyanidins - is often used as a preventive measure against atherosclerosis and venous insufficiency. Up until the publication on April 6, 2000 of German Patent Application No. 19845 314.0, it was not predictable that this food supplement could also specifically be used for the treatment of erectile dysfunction. Surprisingly, it turned out that the proanthocyanidins have a stimulating effect on the endothelial NO-synthase enzyme and thus serves as a stimulator.

The remedy preferably contains a mixture of proanthocyanidins from 50 to 100%, preferably 70%. The effective dosage of proanthocyanidins is 100 to 300 mg, preferably 200 mg, . The dosage amount refers to the daily dose for a male patient weighing 70 kg. For a male patient weighing less than 70 kg, the dosage needed to be effective would be lower and may be as low as 40 mg.

The well known pine bark extract Pycnogenol® food supplement is used as a proanthocyanidins containing remedy for the treatment of erectile dysfunction. In this instance, an application of 125 to 375 mg of Pycnogenol® food supplement is recommended for a 70 kg male.

As mentioned above, nitric oxide and nitric oxide-synthase play an important part in the erectile physiology. Studies with NOS-inhibitors, such as e.g. L-NORAG or L-NAME, which have been injected intracavernally, revealed that an erection induced by electro-stimulations was suppressed. Being afterwards injected intravenally, the natural substrate for NOS, i.e., L-arginine, was able to partly recover the erection (Jung et al., Yonsei Med. J. 1997, 3 (5), 261-269). The simultaneous injection of NOS-inhibitors and L-arginine led to a suppression of the effect of the inhibitors. Although L-arginine as a natural substrate of the endothelial NO-synthase enzyme is - as mentioned previously - able to partly decrease the effect of the NOS-inhibitors, it yet has not been taken into account as a remedy to promote the erectility.

According to the invention, the preferred remedy in addition to the proanthocyanidins also contains L-arginine (or its salts) as an effective component in an amount of at least 0.5 to 2 g. According to the invention, the combination of proanthocyanidins with L-arginine (or its salts) is particularly efficient. The L-arginine (or its salts) is the natural substrate for the nitric oxide synthase.

The active ingredients proanthocyanidins and L-arginine (or its salts) may be taken simultaneously that for maximum effect and benefit in treating erectile dysfunction. In addition, additional ingredients may include further pharmaceutically acceptable auxiliary or carrier substances, so far as they are, for example, used to get the active substance into the shape suitable for the desired medication.

Surprisingly, proanthocyanidins have a selective and specific effect on the blood vessels in the erectile tissue so that a remedy containing proanthocyanidins can preferably be given orally. As such, the remedy according to the invention thus exists in a form suitable for oral medication.

When taken with a known oral treatment remedy for erectile dysfunction, i.e., sildenafil (Viagra), proanthocyanidins help stimulate the endothelial NO-synthase enzyme, which serves as a catalyst for synthesis of nitric oxide from the substrate L-arginine or its salts. The released nitric oxide activates the guanylyl cyclase, leading to an increase in cGMP, which causes relaxation of smooth muscles, which in turn is the condition needed for increased blood supply. Thus, taking proanthocyanidins and L-arginine or its salts would complement the taking of sildenafil (Viagra) in the treatment of erectile dysfunction.

In addition, there are other substances that are available that have the same, or substantially the same, mechanism of action as sildenafil. These other substances, which may be considered inhibitors, are formed to inhibit phosphodiesterase type 5 and/or prevent the decrease of cGMP. The taking of proanthocyanidins and L-arginine (or its salts) would complement these other substances by countering the persistent inability of a man with erectile dysfunction to get an erection and to maintain it long enough for satisfying sexual intercourse.

A clinical study was conducted on forty participants who had erectile dysfunction. The study involved the effect of taking arginine aspartate, which is a salt of arginine with aspartic acid. One gram of arginine aspartate contains 566.85 mg of arginine.

The participants were grouped according to their variant of disturbed erection. The variants are in five categories: weakened, delayed, hesitating, losing and normal. The "weakened" variant signifies that the penis increases in size and becomes hard to a certain extent, but it is not enough to enter the vagina. The "delayed" variant signifies that if it is possible for the penis to become hard enough to enter the vagina, but such may require additional time. The "hesitating" variant signifies that before or after sexual contact, the erection is unstable and thus makes the sexual intercourse more difficult. The "losing" variant signifies that during the love

game there is good erection, but such is lost when trying to make contact or during intercourse.

The "normal" variant signifies that no appreciable disturbed erection was present.

The clinical study was over three months. During the first month, only 3 doses of 1000 milligrams (mg) of arginine aspartate (Sargenor) were administered daily to each participant.

5 By the end of the first month, there was improvement in erectile dysfunction in about 10% of the participants. During the second month, 2 doses of 40 mg of Pycnogenol® food supplement were administered daily to each participant, together with the 3 doses of 1000 mg of arginine aspartate. By the end of the second month, there was a statistically significant improvement of erectile dysfunction in 80% of the participants. During the third month, 3 doses of 40 mg of
10 Pycnogenol® food supplement were administered daily to each participant, together with the 3 doses of 1000 mg of arginine aspartate. By the end of the third month, there was further improvement of the erectile dysfunction condition even for some of the participants who had not shown improvement during the second month. Overall, there was a statistically significant improvement of erectile dysfunction in 92% of the treated participants.

15 The following statistical analysis of the results from the clinical study calculate the probability of whether the observed differences between two treatments are statistically significant at a certain level.

Variants of Disturbed Erection	Before		After 1 month		After 2 months		After 3 months	
	n	D	n	D	n	D	n	D
Weakened	22 (55%)		20 (50%)	NS	5 (12.5%) *		2 (5%)**	
Delayed	12 (30%)		10 (25%)	NS	2 (5%) *		0 (0%)**	
Hesitating	2 (5%)		4 (10%)	NS	1 (2.5%)*		1(2.5%)**	
Losing	4 (10 %)		4 (10%)	NS	0 (0%) *		0 (0%)**	
Normal	0 (0 %)		2 (5%)	NS	32 (80%)***		37(92.5%)**	

* p<0.05

** p<0.01

*** p<0.001

NS = not significant, n = number of participants/patients, D = percent distribution, A = arginine asparatate (each month at 3 doses x 1000 mg daily), P= Pycnogenol® food supplement (2nd month at 2 doses x 40 mg daily, 3rd month at 3 doses x 40 mg daily), p=probability.

In view of the clinical trial results, a dosage between 200 mg and 2 g of arginine per day together with a dosage of 60-360 mg of Pycnogenol® food supplement per day would be a therapeutically effective amount to relieve erectile dysfunction. According to the clinical study, the amount of arginine administered per day was about 1.7 grams, which is computed on the basis that 3 doses were taken of arginine asparatate, with each dose containing 566.85 mg of arginine.

The clinical trial used Caucasian men as the participants and the results show that 80-120 mg of Pycnogenol® food supplement is effective. For men with a lower body weight as compared to Caucasians, such as some Asians, positive results would be expected with a lower

dosage. A dosage as low as 40 mg Pycnogenol® food supplement would be expected to be effective. Also, turning to the higher dosage level, one must consider that a small portion of the population is of tall height and overweight, which is expected to need a higher dosage to be effective. The highest dosage of Pycnogenol® food supplement used so far in other clinical trials (against edema of the lower legs) was 360 mg daily. The dosage of 300 mg is within the dosage range which had been tested clinically and one can expect that men with overweight and oversize need such a higher dose. Therefore, a dosage range of 40 mg - 300 mg of Pycnogenol® food supplement would be effective, with the amount of the dosage that would be effective within the range depending upon the body weight of the man taking it.

Of course the same arguments hold for L-arginine and its salts. For men of lower body weight, a dosage of L-arginine or its salts as low as 200 mg would be effective and for men of greater body weight, a dosage of L-arginine or its salts as high as 2 grams would be effective. Thus, a range of 200 mg to 2 grams of L-arginine or its salts is effective depending upon the body weight and size of the man taking it. The effects of arginine are also dependent on the dosage and on the time elapsed between intake and sexual activity. The clinical study was based on daily intake only and did not specify any particular dosing intervals or prescribe a dosage regimen instruction for the patient participants to take, such as taking a certain amount of arginine at a defined period of time before sexual activity. Such instruction would be expected to better optimize the effectiveness of treating erectile dysfunction with these substances.

The dosage of Pycnogenol® food supplement may be 1-1.5 mg/kg and the dosage of L-arginine may be 15-40 mg/kg, preferably taken simultaneously to maximize their effectiveness in treating erectile dysfunction.

The reference to NO-synthase in this application is with respect to endothelial nitric oxide synthase, as opposed to inducible nitric oxide. The inducible nitric oxide synthase acts in an entirely different way and on a different place as the endothelial nitric oxide synthase.

5 The inducible nitric oxide synthase is produced in macrophages, white blood cells, which use the produced nitric oxide as one of their weapons against virus or bacteria, it is an inflammatory response. The endothelial nitric oxide regulates physiologically the vascular diameter and it is this enzyme which regulates erectile function.

Various changes and modifications may be made to the embodiments without departing from the spirit and scope of the present invention.

I CLAIM:

1. In a stimulation technique, providing both proanthocyanidins as an active ingredient and a substrate L-arginine or its salts as a source of nitric oxide, stimulating an endothelial NO-synthase enzyme with the proanthocyanidins; and releasing the nitric oxide from the substrate L-arginine or its salts in response to the stimulated endothelial NO-synthase enzyme acting as a catalyst for synthesis of the nitric oxide from the L-arginine or its salts, the proanthocyanidins and the substrate L-arginine or its salts each being in therapeutically effective amounts to cause a sufficient amount of the nitric oxide to be released from the synthesis to relieve symptoms of erectile dysfunction.
2. In the stimulation technique according to claim 1, wherein the proanthocyanidins are in an amount of 40 to 300 mg.
3. In the stimulation technique according to claim 1, wherein the L-arginine or its salts is in an amount between 200 milligrams and 2 grams, inclusive.
4. In the stimulation technique according to claim 1, wherein the proanthocyanidins and the L-arginine or its salts are administered simultaneously.
5. In the stimulation technique according to claim 4, wherein the proanthocyanidins are in a dosage of 1-1.5 mg/kg and the L-arginine or its salts is in a dosage of 15-40 mg/kg.

6. In the stimulation technique according to claim 1, further comprising providing the active ingredient in a form suitable for oral administration.
7. In the stimulation technique according to claim 1, wherein the stimulating is also carried out at the same time with sildenafil.
8. In the stimulation technique according to claim 1, wherein the stimulating is carried out while inhibiting an enzyme phosphodiesterase type 5 from reducing an amount of cyclic guanosine monophosphate.
9. In the stimulation technique according to claim 1, wherein the stimulating is carried out while preventing a decrease of cyclic guanosine monophosphate.
10. A combination that includes a substrate L-arginine or its salts as a source of nitric oxide and a stimulator that comprises proanthocyanidins as an active ingredient in an amount effective to stimulate an endothelial NO-synthase enzyme, which serves as a catalyst for synthesis of the nitric oxide from the substrate L-arginine or its salts, the proanthocyanidins and the substrate L-arginine or its salts being in therapeutically effective amounts to cause a sufficient amount of the nitric oxide to be released from the synthesis to relieve symptoms of erectile dysfunction.

11. A combination as in claim 10 in combination with sildenafil as a further active ingredient in a therapeutically effective amount to relieve the symptoms of erectile dysfunction and stimulate the endothelial NO-synthase enzyme.

5 12. A combination as in claim 10 in further combination with an inhibitor effective to inhibit an enzyme phosphodiesterase type 5 from reducing an amount of cyclic guanosine monophosphate.

10 13. A combination as in claim 10 in further combination with substances that are effective to prevent a decrease of cyclic guanosine monophosphate.

14. A combination as in claim 10, wherein the proanthocyanidins are in an amount within a range of 40 mg - 300 mg, inclusive.

15 15. A combination as in claim 10, wherein the L-arginine or its salts is in an amount within a range of 200 mg and 2 grams, inclusive.

16. A combination as in claim 10, wherein the proanthocyanidins are in an amount within a range of 40 mg - 300 mg, inclusive.

20

17. A combination as in claim 10, wherein the proanthocyanidins are in dosage of 1-1.5 mg/kg and the L-arginine or its salts are in a dosage of 15-40 mg/kg.

* * * * *

Box No. VIII (v) DECLARATION: NON-PREJUDICIAL DISCLOSURES OR EXCEPTIONS TO LACK OF NOVELTY

The declaration must conform to the standardized wording provided for in Section 215; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (v). If this Box is not used, this sheet should not be included in the request.

Declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51bis.1(a)(v)):

In relation to this international application, Horphag Research Limited declares that the subject matter claimed in this international application was disclosed as follows:

(i) Kind of disclosure

(a) publication

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(iii) title of disclosure: German disclosure document no. DE19845314 A1

(iv) place of disclosure: German Patent and Trademark Office

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☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (v)".

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MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), **OAPI** patent (BF, BJ, CF,
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 198 45 314 A (ROHDEWALD PETER) 6 April 2000 (2000-04-06) cited in the application claims	1-17
A	WO 99 45797 A (CHEVAUX KATI A ;MARS INC (US); ROMANCZYK LEO J JR (US); SCHMITZ HA) 16 September 1999 (1999-09-16) claims	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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G document member of the same patent family

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 information on patent family members

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